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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/306,662	05/05/1999	MARK K. MALMROS	PRO-SE	3760

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	35

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/306,662	MALMROS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 Mar 2002, 08 Jul 2002, 23 Aug 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5 and 7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5 and 7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *25,31,33* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS (PTO-1449) Paper No. 34* .

Detailed Action

1. The amendment filed on March 2, 2002 in Paper No. 26 is acknowledged and has been entered. Claims 12, 13, and 17-19 have been canceled. Claims 1, 5, and 8-11 have been amended.

2. The amendment filed on July 8, 2002 in Paper No. 28 is acknowledged and has been entered. Claim 7 has been amended.

3. The supplemental response filed August 23, 2002 in Paper No. 32 is acknowledged and has been entered.

4. Claims 1, 5, and 7-11 are pending in the application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

5. Unless specifically reiterated below, the grounds of rejections and objections set forth in the previous Office action mailed November 26, 2001 (Paper No. 18) are withdrawn.

Grounds of Claim Rejections Maintained and Reply to Applicants' Remarks

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 5, and 7-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1, 5, and 7-11 are vague and indefinite because presently claim 1 recites the phrase "comparing the degree of the metachromatic shift of the dye from the

reflected light spectrum of the stained tissue or cells with the degree of the metachromatic shift of the dye from a library". Despite the amendment to claim 1, it is still not clear how the spectra are to be compared; in other words, it is not clear what aspect or characteristic of the spectrum are to be compared with the library of previously obtained spectra. The terms "the metachromatic shift" and "the degree of the metachromatic shift" appear not to be defined in the specification. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

(b) Claims 1, 5, and 7-11 are vague and indefinite because presently claim 1 recites the phrase, "with a library of previously obtained spectra of similarly stained tissue or cells". Recitation of the phrase renders the claim vague and indefinite because it cannot be determined from which similarly stained tissue or cells said library of previously obtained spectra is to be obtained prior to steps (a)-(d) and from what source said similarly stained tissue and cells are to be derived. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

(c) Claims 1, 5, and 7-11 are vague and indefinite because claim 1 recites the phrase "correlating the reflected light spectrum with a disease state". Recitation of the phrase renders the claim vague and indefinite because it cannot be ascertained how the correlating the reflected light spectrum with a disease state leads to a diagnosis of a dysplasia, pre-cancer, or cancer in a living organism. How is the spectrum of reflected light and disease state related? Is this relationship true of every type of spectrum of reflected light generated by either methylene blue or toluidine blue O? Is the relationship true of every type of disease state? In other words, it is unclear how the method is to be used to meet the objective recited in the preamble of the claim. Finally, how is the disease state to which reflected light spectrum to be correlated related to dysplasia, pre-cancer, or cancer? Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicants' amendment and their remarks have been carefully considered, but have not been found to obviate these grounds of rejection, which were set forth in the previous Office action mailed November 26, 2001 (Paper No. 18).

New Grounds of Claim Rejections

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 5, and 7-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites "the degree of the metachromatic shift of the dye from the reflected light spectrum of the stained tissue or cells" and "the degree of the metachromatic shift of the dye from a library". However, there does not appear to be proper and sufficient antecedent basis in the specification for recitation of these phrases, terms, and/or limitations in the claims. Therefore, the recitations appear to introduce new matter and thereby violate the written description requirement set forth under 35 USC § 112, first paragraph.

This matter might be resolved, however, if Applicants were to point to particular passages in the specification that are believed to provide the necessary support for the recitations.

10. Claims 1, 5, and 7-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 5, and 7-11 are indefinite because claim 1 recites the term "similarly stained tissue or cells". Recitation of this term renders the claims indefinite because it cannot be ascertained how similarly the different tissue or cells must be stained. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 10 recites the limitation "wherein the tissues or cells are from at least one organ selected from the group consisting of skin, cervix, vagina, mouth, colon, esophagus and internal organs". Recitation of the limitation renders the claim indefinite because at least the cervix, colon, and esophagus are internal organs.

Claim Rejections – 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 1, 5, and 7-11 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by US Patent No. 5,784,162-A, as evidenced by Vaezy, et *al (Journal of Microscopy* **163**: 85-94, 1991) and Marchesini, et *al (Photochemistry and Photobiology* **55**: 515-522, 1992) for the reasons set forth in the previous Office action mailed November 26, 2001 (Paper No. 18).

Applicants have traversed the grounds of this rejection in Paper Nos. 26 and 32. Applicants' arguments have been carefully considered but have not been found persuasive.

The prior art teaches the use of a combination of dyes; one of which is methylene blue.

In reply to Applicants' argument that the prior art relates to detecting spatial organization or distribution and quantifying the cellular or tissue constituents, as opposed to diagnosing cancer, the prior art teaches, "morphometric spectal image analysis enables evaluation of subtle cytological and histological features to yield useful ultrastructural and medical information for diagnostic and prognostic evaluation" (column 37, lines 28-32). Furthermore, the prior art teaches the SpectraCube™ system combined with the methods of the claimed invention enable the artisan to monitor developmental changes occurring in a healthy tissue. The prior art discloses, "[s]ince various malignancies are also characterized by unique developmental features, the SpectraCube™ system and the methods of the present invention can be adopted to monitor these characterizing features and thus to assist in for example early diagnosis (e.g., existence and stage) of such malignancies" (column 45, lines 35-43). In fact, in Example 8, the prior art discloses an example in which the SpectraCube™ system and the methods of the claimed invention were used to differentiate a cancerous cell from a normal cell.

In reply to Applicants' argument that the methods of the prior art are not in situ methods, claim 3, for example, recites the limitation "wherein said optical device is [...] an endoscope", which is an instrument used to examine tissue or cells *in situ*. Although the prior art exemplifies the examination of a sample collected by a "Pap smear", it is

evident that the methods of the prior art can be used to diagnose cancer *in situ*. The prior art discloses that the sample may be any biological sample, including a whole organism (column 40, lines 1-3).

In reply to Applicants' argument that the prior art teaches that transmission microscopy suffers greatly from the inherently low contrast of cell organelles and structural details, the prior art teaches "[t]he use of the spectral bio-imaging methods of the present invention is one of the most straightforward methods to increase the apparent contrast of cells and tissues examined under a transmission microscope, thereby improving dramatically the identification and discrimination capabilities of this popular microscopic method" (column 36, lines 22-27). In reply to Applicants' remark that the prior art teaches that one advantage of combining spectral bio-imaging and transmission microscopy is the ability to use a "clean" measurement technique, the prior art teaches *in some cases*, there is no need to use potentially toxic dyes or fixation agents (column 39, lines 10-16).

In reply to Applicants' argument that one skilled in the art would not recognize that the metachromatic properties of the dyes used in the methods of the prior art enable differentiation and diagnosis, the artisan would understand that the dyes differentially stain cancerous and normal tissue such that the differences can be characterized by comparing the absorption or transmission spectra of the two types of dye-stained tissues. "Metachromasia" is no more than a fanciful way of describing the change in the absorption or transmission spectrum of a dye that occurs after staining two different types of tissue or cells. The "metachromatic shift of the dye" to which the claims refer, thus, is interpreted to denote the change that is observed in the transmission spectrum of a dye after staining a particular tissue or cell relative to that which was previously observed after staining another tissue or cell, or relative to a composite of transmission spectra observed after staining a library of tissues or cells. Moreover, the change in the absorption or transmission spectra of a dye, or the metachromatic shift is an inherent property of the dye. Therefore, in response to Applicants' argument that the prior art does not teach or suggest quantifying the metachromatic shift of a dye and correlating the presence of a shift with the presence of

cancerous cells or tissue, contrary to Applicants' remarks, the prior art does teach methods that differentiate cancerous tissue and normal tissue on the basis of differences or similarities that are observed in the transmission spectra of a dye after staining a sample containing suspected cancerous cells and a library of tissues or cells that have been previously characterized as either cancerous or not. In practicing the method of the prior art, the artisan necessarily determined the metachromatic shift of the dye that was used to stain the tissues or cells.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 5, and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,784,162-A in view of Tuite, et al (*Journal of Photochemistry and Photobiology B: Biology* 21: 103-124, 1993), as evidenced by Vaezy, et *al (Journal of Microscopy* **163**: 85-94, 1991) and Marchesini, et *al (Photochemistry and Photobiology* **55**: 515-522, 1992).

US Patent No. 5,784,162-A ('162) teaches methods for using a combination of dyes comprising methylene blue, but does not teach the use of toluidine blue O.

Tuite, et al teach that toluidine blue O and methylene blue can selectively stain tumor cells and are generally non-toxic to normal cells.

Given the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used toluidine blue O in the methods of '162, because both methylene blue and toluidine blue had been characterized as non-toxic and known to selectively stain cancer cells. One of ordinary skill in the art at the time the invention was made would have been motivated

to use toluidine blue in the methods of '162 to confirm the results of analyses in which methylene blue had been used.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 10, 2002